## STATISTICAL REVIEW AND EVALUATION

6/30/98

**ORIGINAL PLA #**: 97-1052

**SPONSOR**: SKB

**NAME OF PRODUCT**: Lyme Disease vaccine (Lymerix)

**DOCUMENT REVIEWED**: two FAX documents; #1- 52 pages
#2 - 86 pages

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File:OV-4.7, Original PLA, Lyme disease vaccine

### BACKGROUND

During a telecon on May 13, SKB notified CBER that there were specific concerns regarding CMI issues and the possibility that the OspA portion of the protein in their Lyme vaccine could induce a chronic-resistant form of arthritis in some individuals. Technical issues regarding the genetic predisposition for autoimmune arthritis in individuals with specific HLA alleles ( — allele) and /or past history of arthritis and similar joint symptoms ensued. Of particular importance was the VRBPAC meeting which was scheduled to occur two weeks later. A scientific manuscript which proposed these relationships had been authored by the PI of the Lyme efficacy study (Dr. Allen Steere), and had been accepted by *Nature* for an imminent publication date. CBER requested the submission of all analyses conducted by the DSMB to address arthritis issues throughout the course of the Lyme008 Phase III efficacy study. These studies were described in PLA review materials, but not specifically submitted. The SKB DSMB

was quickly reconvened to address the issues of Steere, and were prepared to comment at the VRBPAC, as necessary. The CBER Lyme committee met continuously through the subsequent two weeks preceding Advisory, in order to re-review and analyze all materials that had been part of the PLA regarding points that might relate to the new findings while awaiting the DSMB analyses, and to provide extra scrutiny of a variety of separately reported symptoms. The committee agreed that while there were not consistent group differences among those who had received vaccine vs placebo among reviewed materials, additional information should be sought. Meetings with Drs. Hardegree and Zoon of CBER and then the Commissioner of FDA (acting-Freidman) advised of our understanding of the key positions of both Dr. Steere and the sponsor. Additional materials were requested of the sponsor, referred to herein as "FAX 1 and FAX 2", which arrived at CBER 2 days before the scheduled VRBPAC meeting.

**Review- FAX #1 (aka Part 2 per SKB)**

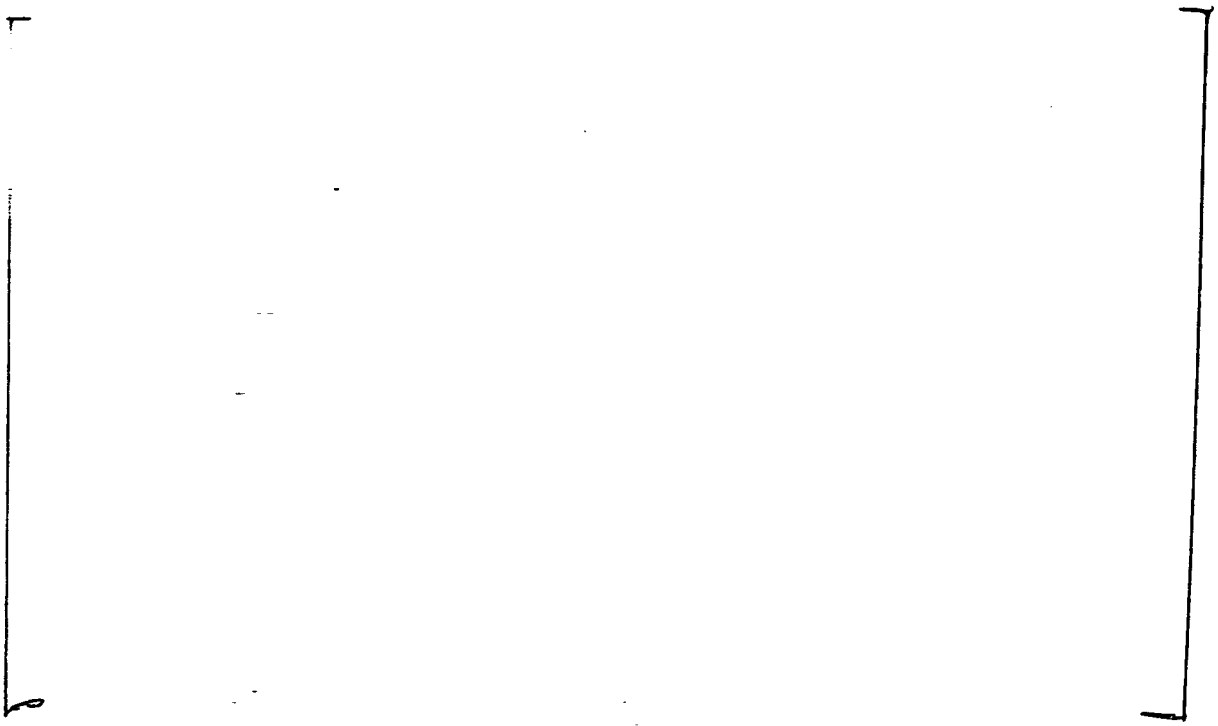
Several different questions were posed to SKB during the May 13 telecon and are reviewed here under the separate FAX transmissions. The sponsor was asked to provide — for each year for different case definition groupings. These were provided and are correctly calculated.

Next, SKB was asked to provide solicited reactogenicity data, focusing on arthralgia reports, which included information on such arthralgia cases which lasted longer than 24 hours. In the PLA the sponsor had selected to report such information only in terms of early occurrence, described as 'within 24 hours post-dose'. The review document states that the Tables 5?.50c/d provide a summary of local and general symptoms by duration for subjects in the specific Center (24) used to obtain such data, with the second table providing a listing of arthralgias lasting longer than three days along with the investigator's attribution of relationship to vaccination. ——————

——————— While it is less clear where the aggregate discrepancies may arise for Table 5?.50c/d, in Table 5?.50e more obvious errors are apparent on individual subject bases. First, the duration which is shown in the Table frequently does not correspond to what is provided in the IPP. For example, Subjects——— and ———have FAX tables values for duration of 236, 32 and 4 days, while the PLA IPP records for these patients and these symptom durations indicate 233,28 and 1 days, respectively. The heading for this Table reads: listing of subjects with arthralgia symptoms lasting more than 3 days. For one patient ( —— ) an arthralgia occurring after the third dose and lasting more than 4 days is not included. There are more examples of this situation. For two subjects listed in the first table on page 004 (# — . and — ) their symptoms are noted as 'ongoing', yet in FAX2 as reviewed below, they are missing from the subsets of patients sent by Dr. Steere to the DSMB for review (see ref. "List 107) as well as from

the more comprehensive review list derived from multiple sources (see ref. "List 304").

As an example of a different problem, only one patient (# ——) from among either the vaccine or placebo recipients provided in these two tables is among the patients referred to the DSMB (List 107) as having "new onset" symptoms defined as joint symptoms which developed "within one month of vaccination and lasting at least one month". Unfortunately, closer inspection indicates this patient's duration was only 4 days with an 'unrelated' investigator attribution. When using the sponsor's duration tabulation, it is not clear why other patients (for example, # ——— and ——— from the vaccine group and # ——— and ——— from the placebo group) were not a part of this List.



The sponsor has provided in Table 5C.c the incidence of arthritis occurring within 30 days of vaccination. The tabulation includes only the terms 'arthritis', 'arthritis aggrevated' (sic), and 'arthrosis'.

**Comment: Please provide the information in your Table 5C.c for the terms 'arthralgia', 'arthropathy' and 'myalgia'. Please also provide, for all of the terms, the same comparison for unsolicited AEs occurring later than 30 days post-vaccination.**

On page 007, SKB has provided Table 5F.a&b which were requested to provide the incidence and duration of mild and moderate solicited events not included in the PLA review materials. The symptoms are shown by dose, as aggregate totals and further cross-classified for duration >24 vs <24 hours, and displayed separately for mild and

moderate. The individually tabulated n and % are frequently discrepant from aggregate information in Volume 25 which displays these symptoms. Chi square comparisons of several 'mild' symptoms (arthralgia and rash in general and fatigue post dose 2) show significant group differences. Among the moderate tabulations, there appear to be important groups differences for the longer duration category for both arthralgia and fatigue.

On page 009, SKB provides re-tabulated ITT efficacy information, all of which is correct. On page 010, the sponsor provides a cross tabulation of subjects enrolled in their 15-18 year old cohort by vaccine group. This is correct information.

On page 011, SKB was asked to provide a mechanism for CBER to assess the representativeness of the subset of subjects at Center 24 used for solicited reactogenicity and other safety and immunogenicity analyses. To this end, CBER was provided with all solicited and unsolicited AEs for the ITT population at this Center. Various conceptual inconsistencies regarding the numbers provided in the tables, are noted.

**Comment: Table 1 on page 011 shows subjects with solicited AEs (ITT). There were 465 vaccinees and 463 placebo recipients, and for arthralgia, for example, there were 26 and 16 cases noted in each respective group. However, in the solicited ATP values provided to us on page 004, Tables 5?.50c/d which only includes 402 vaccinees and 398 placebo subjects, there would appear to have been many more cases related to the number of symptoms. Specifically, your Table 1 indicates only 5-6% arthralgia's among the vaccinees at this Center, while the percentage is approximately 25-26% for the solicited reactogenicity ATP cohort (PLA Vol. 25, Tables 39 & 42).**

**Also, we note that the n/group for the ITT vaccinees and placebos appear to be missing 5 subjects in each group as presented in Table 1 on page 011 (465V, 463P), as opposed to subsequent Tables utilizing these subgroups on page 012-029. In the tables of these latter pages there are 470 and 468 subjects in each of**

these groups.

On page 30, SKB provided a table (1?.9) to depict the cross-classification of subjects who had a history of Lyme disease at study entry (LD) and those who were "WB positive at baseline". Review data was able to verify the subjects who were WB+ as n=250, but could not verify or easily classify from the eCRFs (IPP) data the subjects who reported a history of LD. The protocol stated that the only subjects who would have baseline WB tests were those for whom a month 12 serology was WB+ or those who were tested for suspect Lyme.

**When reclassifying (if necessary) these subjects, please provide an electronic file which contains a listing of the PIDs for:**

- **all vaccinees with WB+ at baseline and LD history (n = 60)**
- **all placebos with WB+ at baseline and LD history (n=59)**
- **all vaccinees AND placebos with LD history for whom no baseline WB Is available**

**In a telecon we had requested the name of the file and the variable(s) which may be used in the current PLA review materials (SAS transport files) to identify the patients with "LD history".**

**Please also submit as electronic data, a file containing the PIDs for all subjects classified as "LD history" as described in the PLA. Please submit an analysis of your choice that demonstrates any relationship between the following variables: prior LD history, prior/current history of joint symptoms (to include:arthralgia, arthritis, arthropathy, arthrosis, myalgia**;nb clinical; check for comprehensiveness of this symptom list for purpose), **and occurrence of any of these symptoms at any time in the trial, analyzed by dose.**

On pages 31-36, the sponsor has provided statistical comparisons of early AE incidence among vaccinees with positive and "negative" WB at baseline. Given the

inaccurate use of the WB- term and classification of patients, these analyses will need to be repeated.

**Comment: Please provide new analyses for those provided on your pages 31-36, utilizing only those patients with baseline WB test results. Please also provide these comparisons for the placbo subjects.**

Data provided on pages 37-42 which compares early AEs between subjects with and without LD history, indicates only a few areas of significant difference, whereas for late AE there are several. This trend is also true when observing the comparisons for these groups regarding *frequent* early vs late symptoms.

[redacted]

**FAX #2 - (aka Part 1 per SKB)**

SKB convened it's DSMB on two specific occasions to investigate issue regarding arthritis and various aspects of joint problems and arthriric disease processes. Data from two different sets of patients (List 107) and (List 304) were sent at different intervals for blinded A/B analyses intended to detect an excess of symptomatology ascribed to such AEs in either arm of the study. The PLA review materials did not include the data for these analyses, and the sponsor was queried to provide more information about these analyses and the DSMB conclusions.

[redacted]

for List 107 patients, although three sets of analyses accompany that for List 304 patients. [

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After unblinding the study, the DSMB was asked to 'blindly' evaluate a second group of 304 subjects (LIST 304) for possible association with inflammatory arthropathy. This group of 304 subjects represented 328 unique classifications of either "late onset event = arthritis", SAE=arthritis, or a Steere evaluation of 'inflammatory arthropathy'. SKB noted there was overlap among these classifications. A questionnaire "was also" sent to each investigator to obtain additional information on patients. This implies that the 304 were first collated in some manner and then these same classification symptoms and others were solicited from investigators directly. Some form of all of this information was then compiled by someone and presented to three DSMB members. These members were asked to classify each of 304 (LIST 304) subjects according to five variables related to arthritis, one of which was duration of symptoms. A re-randomization scheme was used to keep members 'blind' to original group identifiers. Results indicated no evidence of differential A/B symptom distributions, however, inspection of the cross tabulations produced from the ratings of each member, indicated complete discordance

in ratings for the same patients, including such variables as duration.

[redacted]

[redacted]

I hand-entered each PID and group variable from the hardcopy FAX, and produced an analysis to discern how many patients from FAX #1, List 107 and List 304 might be overlapping as subsets. Given the definitions that were supposedly used to produce these sets, an unacceptably small number of patients were co-represented in these databases.

Subjects in FAX#1 and List 107: (n=1) ——
Subjects in FAX#1 and List 304: (n=4) ————————
Subjects in List 107 and List 304: (n=14) ————————————————————

**Comment: subject inclusion in these three databases does not appear to have been done in a standard manner. None of the long duration arthralgias from Center 24 were included in the List 107, yet one patient with 'unrelated' symptoms and short duration (#——) was included.** [redacted]

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